NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 429

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIETHYLPHTHALATE (CAS NO. 84-66-2) IN F344/N RATS AND B6C3F$_1$ MICE

(DERMAL STUDIES)

with

DERMAL INITIATION/PROMOTION STUDY OF DIETHYLPHTHALATE AND DIMETHYLPHTHALATE (CAS NO. 131-11-3) IN MALE SWISS (CD-1®) MICE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

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P.O. Box 12233
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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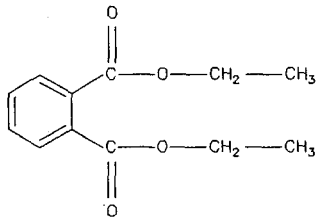
ABSTRACT

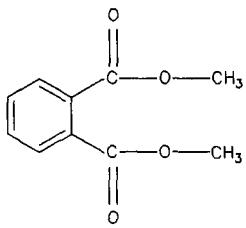


DIETHYLPHTHALATE

CAS No. 84-66-2

Chemical Formula: $C_{12}H_{14}O_4$ Molecular Weight: 222.26

Synonyms: 1,2-benzenedicarboxylic acid, diethyl ester; DEP; diethyl 1,2-benzenedicarboxylate; diethyl *o*-phthalate; diethyl phthalate; ethyl phthalate; *o*-benzenedicarboxylic acid diethyl ester; phthalic acid, diethyl ester; RCRA U088
Trade Names: Anozol; DPX-F5384; Estol 1550; Neantine; Palatinol A; Phthalol; Placidol E; Solvanol; Unimoll DA



DIMETHYLPHTHALATE

CAS No. 131-11-3

Chemical Formula: $C_{10}H_{10}O_4$ Molecular Weight: 194.19

Synonyms: 1,2-benzenedicarboxylic acid, dimethyl ester; dimethyl 1,2-benzenedicarboxylate; dimethyl benzene-*o*-dicarboxylate; dimethyl benzeneorthodicarboxylate; dimethyl *o*-phthalate; dimethyl phthalate; DMP; FIFRA 028002; methyl phthalate; *o*-dimethyl phthalate; phthalic acid, dimethyl ester; phthalic acid methyl ester; RCRA U102
Trade Names: Avolin; DMF (insect repellent); ENT 262; Fermine; Mipax; NTM; Palatinol M; Repeftal; Solvanom; Solvarone; Unimoll DM

Diethylphthalate and dimethylphthalate are used as phthalate plasticizers, in an extensive array of products. The chronic dermal toxicity of diethylphthalate was evaluated in male and female F344/N rats and B6C3F$_1$ mice in 2-year studies. In a series of special studies, the tumor initiation or promotion potential of diethylphthalate or dimethylphthalate was evaluated in male Swiss (CD-1®) mice by an

initiation/promotion model of skin carcinogenesis. The genetic toxicity of diethylphthalate and dimethylphthalate in *Salmonella typhimurium* and cultured Chinese hamster ovary cells was also evaluated.

4-Week Study In F344/N Rats

Groups of 10 male and 10 female rats were dermally administered diethylphthalate at volumes of 0, 37.5, 75, 150, or 300 μL (0, 46, 92, 184, or 369 μg) applied neat, 5 days per week for 4 weeks. All male and female rats survived to the end of the study. No evidence of dermatotoxicity was observed, with no adverse clinical signs observed and no effects on weight gain or feed consumption. Relative liver weights of 300 μL males and females and 150 μL females were greater than those of controls. Relative kidney weights of 150 and 300 μL males and 150 μL females were greater than those of controls. No other adverse effects were observed in this study.

4-Week Study In B6C3F$_1$ Mice

Groups of 10 male and 10 female mice were dermally administered diethylphthalate at volumes of 0, 12.5, 25, 50, or 100 μL (0, 15, 31, 62, or 123 μg) applied neat, five days per week for 4 weeks. One control female died before the end of the study; all other mice survived. No evidence of dermatotoxicity or other adverse clinical signs were observed, and no clear adverse effects on weight gain or feed consumption were seen. Absolute and relative liver weights of 25 and 100 μL females were greater than those of the controls. Based on these 4-week study results, doses of 0, 35, and 100 μL diethylphthalate were recommended for the 2-year mouse studies. A chronic study in male and female B6C3F$_1$ mice at 0, 35, and 100 μL (applied neat, once per day, 5 days per week) was started and subsequently stopped after 32 weeks when significant body weight reductions were noted in treated animals (males and females, 100 μL groups: 19% lower; males, 35 μL group: 12% lower; females, 35 μL group: 10% lower than controls). Based on these body weight reductions, doses of 0, 7.5, 15, and 30 μL in 100 μL acetone were recommended for the restart of the 2-year mouse study.

2-Year Study In F344/N Rats

Based upon the results of the 4-week study, doses of 0, 100, or 300 μL diethylphthalate (0, 123, or 369 μg) were chosen for the 2-year rat study. Groups of 60 male and 60 female rats received the doses applied neat 5 days per week for 103 weeks and up to 10 animals per group were evaluated after 15 months.

Survival, Body Weights, and Clinical Findings

Survival of dosed rats during the first 15 months was similar to that of controls. However, 2-year survival was significantly reduced in all groups of male rats (survival probabilities, males: 0 μL, 8%; 100 μL, 12%; and 300 μL, 12%). The mean body weights of 300 μL males were slightly less than those of the controls throughout the study. No adverse clinical signs were observed, including no evidence of dermatotoxicity.

Pathology Findings

No morphological evidence of dermal or systemic toxicity was observed in male or female rats. Skin neoplasms were not observed in female rats and were only rarely observed in male rats. A high incidence of anterior pituitary adenoma occurred in all groups of male and female rats. The incidence of anterior pituitary adenomas in the 0, 100, and 300 μL groups were: males, 39/44, 41/49, 41/49; females, 38/50, 33/49, 33/48. The incidence of this benign tumor in control males (84%) exceeded the historical control mean incidence [feed controls, (28.7%)] and range (12% to 60%). Anterior pituitary adenomas were considered a primary contributing factor in the increased mortality observed in all groups, regardless of treatment. A dose-related decreasing trend in the incidence of mammary gland fibroadenomas was observed in female rats (21/50, 12/48, 7/50). The incidence of mononuclear cell leukemia in male rats in this study was lower than the historical incidence and may be attributable to the shortened life span of male rats. Similarly, the incidence of interstitial cell tumors of the testes was markedly decreased in all groups of males (4/50, 3/50, 8/50), relative to historical control rates (90.1%; range 74%-98%). The incidence of fatty liver degeneration was notably lower in dosed rats than in controls (males: 26/50, 8/50, 4/51; females: 23/50, 11/50, 3/50).

2-Year Study In B6C3F$_1$ Mice

Groups of 60 male and 60 female mice received doses of 0, 7.5, 15, or 30 μL diethylphthalate (0, 9, 18, or 37 μg) in 100 μL acetone 5 days per week for 103 weeks with a 1 week recovery period, and up to 10 animals per group were evaluated after 15 months.

Survival, Body Weights, and Clinical Findings

Two-year survival of dosed mice was similar to that of controls: 43/50, 41/48, 46/50, and 43/50 (males), and 41/50, 38/51, 37/49, and 36/49 (females). Mean body weights of dosed male and female mice were similar to those of the controls throughout the study. No adverse clinical signs were observed in mice, including no gross evidence of dermatotoxicity. Feed consumption by male and female mice was similar to or up to 13% greater than that by controls.

Pathology Findings

No morphological evidence of dermal toxicity was observed in male or female mice. No skin neoplasms were observed in dosed male mice. In female mice receiving 30 μL, one squamous cell carcinoma and one basal cell carcinoma were seen at the site of application. An increased incidence of liver neoplasms was observed in dosed male and female mice. The incidence of hepatocellular adenoma or carcinoma (combined) in B6C3F$_1$ mice in the 0, 7.5, 15, and 30 μL groups were: (males) 9/50, 14/50, 14/50, and 18/50; (females) 7/50, 16/51, 19/50, and 12/50. The incidence of adenoma or carcinoma (combined) was increased in 30 μL male mice and the incidences of adenoma and of adenoma or carcinoma (combined) were increased in 7.5 and 15 μL females. A positive dose-related trend in the incidence of adenoma or carcinoma (combined) was also observed in male mice. The incidence of basophilic hepatic foci was increased in 15 μL male mice (0/50, 1/50, 9/50, 3/50). The increased incidence of liver neoplasms in this study was considered equivocal because the incidence of hepatocellular neoplasms in control and dosed males was within the historical range and because there was no clear dose-response relationship in females. No other treatment-related findings were observed in this study.

1-Year Initiation/Promotion Study In Male Swiss (CD-1®) Mice

Groups of 50 male mice were dosed dermally with diethylphthalate or dimethylphthalate to study their effect as initiators and promoters. Diethylphthalate and dimethylphthalate were tested as initiators with and without the known skin tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA). Diethylphthalate and dimethylphthalate were tested as promoters with and without the known skin tumor initiator 7,12-dimethylbenzanthrancene (DMBA). Comparative control groups used during the study of diethylphthalate and dimethylphthalate included: vehicle control (acetone/acetone); initiation/promotion control (DMBA/TPA); initiator control (DMBA/acetone); and promoter control (acetone/TPA).

Based on the incidence of skin neoplasms diagnosed histologically and the multiplicity of skin neoplasms, there was no suggestion that either diethylphthalate or dimethylphthalate was able to initiate skin carcinogenesis when chronically promoted by TPA. Further, there was no evidence that either diethylphthalate or dimethylphthalate was able to promote skin carcinogenesis in skin previously initiated with DMBA. High incidences of both squamous cell papillomas and squamous cell carcinomas occurred among the initiation/promotion control animals initiated with DMBA and promoted with TPA. All TPA-dosed groups had significantly greater incidences of dermal acanthosis, ulceration, exudation, and hyperkeratosis than controls.

Genetic Toxicology

Neither diethylphthalate (10-10,000 μg/plate) nor dimethylphthalate (33-6,666 μg/plate) induced gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without rat and hamster liver S9. In cultured Chinese hamster ovary cells, both diethylphthalate and dimethylphthalate induced sister chromatid exchanges in the presence of S9. Neither induced sister chromatid exchanges in the absence of S9. Neither chemical induced chromosomal aberrations, with or without S9, in cultured Chinese hamster ovary cells.

Conclusions

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of diethylphthalate in male or female F344/N rats receiving 100 or 300 μL. The sensitivity of the male rat study was reduced due to low survival in all groups. There was *equivocal evidence of carcinogenic activity* of diethylphthalate in male and female B6C3F$_1$ mice based on increased incidences of hepatocellular neoplasms, primarily adenomas.

In an initiation/promotion model of skin carcinogenesis, there was no evidence of initiating activity of diethylphthalate or dimethylphthalate in male Swiss (CD-1®) mice. Further, there was no evidence of

promotion activity of diethylphthalate or dimethylphthalate in male Swiss (CD-1®) mice. The promoting activity of TPA following DMBA initiation was confirmed in these studies.

Minor dermal acanthosis was observed following dermal application of diethylphthalate in male and female F344/N rats dosed for 2 years and in male Swiss (CD-1®) mice dosed for 1 year.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Diethylphthalate

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 100, or 300 μL diethylphthalate applied dermally	0, 100, or 300 μL diethylphthalate applied dermally	0, 7.5, 15, or 30 μL diethylphthalate per 100 μL of acetone applied dermally	0, 7.5, 15, or 30 μL diethylphthalate per 100 μL of acetone applied dermally
Body weights	High-dose group less than controls	Dosed groups similar to controls	Dosed groups similar to controls	Dosed groups similar to controls
2-Year survival rates	4/50, 6/50, 6/51	30/51, 28/50, 23/50	43/50, 41/48, 46/50, 43/50	41/50, 38/51, 37/49, 36/49
Nonneoplastic effects	Skin site of application: acanthosis (2/50, 5/50, 21/51); Liver: fatty degeneration (26/50, 8/50, 4/51)	Skin site of application: acanthosis (8/50, 18/49, 23/50); Liver: fatty degeneration (23/50, 11/50, 3/50)	Liver: basophilic foci (0/50, 1/50, 9/50, 3/50)	None
Neoplastic findings	None	None	None	None
Uncertain effects	None	None	Liver: hepatocellular adenoma (6/50, 11/50, 9/50, 12/50); hepatocellular adenoma or carcinoma (9/50, 14/50, 14/50, 18/50)	Liver: hepatocellular adenoma (4/50, 12/51, 14/50, 10/50); hepatocellular adenoma or carcinoma (7/50, 16/51, 19/50, 12/50)
Level of evidence of carcinogenic activity	No evidence	No evidence	Equivocal evidence	Equivocal evidence
Genetic toxicology				
Salmonella typhimurium gene mutation:	Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Positive with S9; negative without S9			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on diethylphthalate/dimethylphthalate on November 16, 1993, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On November 16, 1993, the draft Technical Report on the toxicology and carcinogenesis studies of diethylphthalate/dimethylphthalate received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. D.S. Marsman, NIEHS, introduced the toxicology and carcinogenesis studies of diethylphthalate and the initiation/promotion studies of diethylphthalate and dimethylphthalate. He discussed the uses of the chemical and the rationale for both studies, described the experimental designs, reported on survival and body weight effects, and commented on compound-related nonneoplastic lesions in male and female rats and male mice in the initiation/promotion study, and the compound-related neoplastic lesions in male and female mice in the 2-year studies. The proposed conclusions were *no evidence of carcinogenic activity* of diethylphthalate for male and female F344/N rats and *equivocal evidence of carcinogenic activity* of diethylphthalate for male and female B6C3F$_1$ mice. In an initiation/promotion model of skin carcinogenesis, there was no evidence of initiating or promoting activity of diethylphthalate or dimethylphthalate for male Swiss (CD-1®) mice.

Dr. Bailey, a principal reviewer, agreed with the proposed conclusions. He said the rationale for dermal application should be expanded since the main routes of exposure for humans appear to be ingestion and inhalation. Dr. Marsman said a 4-week diet study was done and a 2-year diet study was designed, but the dermal route was considered to be the most important route for humans. Dr. Bailey said a comment should be added in the discussion concerning the possibility of ingestion of diethylphthalate from grooming after dermal application. Dr. Marsman agreed that grooming might have resulted in systemic availability of chemical.

Dr. van Zwieten, the second principal reviewer, agreed with the proposed conclusions. He said a comment was needed as to why 4-week studies were done in rats and mice instead of the customary 13-week studies that might have better predicted doses for the first 2-year study in mice. Dr. Marsman said a 4-week prechronic regimen for dermal studies was preferred at the time these studies were initiated, and agreed that 13-week studies might have been more helpful in setting doses for the 2-year mouse studies. Dr. van Zwieten asked for discussion about whether an increased incidence of pituitary neoplasms might help explain the reduced survival in male rats. Dr. J.R. Hailey, NIEHS, commented that many of these neoplasms in males were quite large and could have contributed in an additive way to decreased survival along with nephropathy, which is much more severe in male rats.

Dr. Ryan, the third principal reviewer, had similar questions about choice of dermal exposure over other routes of exposure, and why 4-week instead of 13-week studies were done. She thought the dose-finding aspects for the 2-year studies to be less stringent than usual, expressing doubts that a maximum tolerated dose was reached for either rats or mice.

Dr. Ward asked whether there was evidence of peroxisome proliferation in the livers of animals in any of the studies. Dr. Marsman replied that this was not measured, although the hepatomegaly present could be suggestive of such an effect. Dr. R. David, Eastman Kodak Company, stated that they agreed with the proposed conclusions for rats but thought the proposed conclusions for mice should have been *no evidence* based in part on the incidence of hepatocellular neoplasms in treated male mice being within the historical control range, and on the lack of a dose response for liver neoplasms in female mice.

Dr. Bailey moved that the Technical Report on diethylphthalate and diethylphthalate/dimethylphthalate be accepted with the revisions discussed and with the conclusions as written for the 2-year studies for male and female rats, *no evidence of carcinogenic activity*, and for male and female mice, *equivocal evidence of carcinogenic activity*, as well as the conclusions that there was no evidence of initiating or promoting activity of diethylphthalate or dimethylphthalate in male Swiss (CD-1®) mice. Dr. Ward seconded the motion, which was accepted unanimously with five votes.